Functional Diversity of Histamine and Histamine Receptors

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In order to analyze the mechanisms by which a single biogenic amine like histamine is capable of inducing a wide variety of both physiologic and pathologic functions in various tissues/cells, histamine responses were dissected in detail from a biochemical and pharmacologic point of view. Histamine is synthesized by multiple isozymes of histidine decarboxylase, and catabolized by either diamine oxidase or histamine-N-methyltransferase. Synthesized intracellular histamine may play a role in cell proliferation, whereas released histamine binds to at least three different histamine-specific receptors, then activates various intracellular components, such as Ca^{++}, cAMP, protein kinase, and ion channels. These second messenger pathways interact differentially with each other in various tissues/cells. Moreover, histamine not only activates its own receptors, but also activates other related receptors such as the serotonin 1c receptor. Therefore, to understand the complex actions of histamine, new approaches should be established, in which multiple phenomena can be monitored simultaneously. *J Invest Dermatol 98:8S–11S, 1992*

Histamine is known to exhibit a wide variety of both physiologic and pathologic functions in different tissues and cells, and also appears to serve as a neurotransmitter/neuromodulator in the brain [1]. Histamine action is believed to be mediated by binding to its specific cell-surface receptors. Extensive pharmacologic analysis identifies at least three different subtypes of histamine receptors using highly specific competitive agonists and antagonists. The H_1 histamine receptor is mainly involved in smooth muscle contraction and vascular permeability [2]. The H_2 receptor mediates gastric acid secretion [3], whereas the H_3 receptor is present at pre-synaptic locations in the central nervous system and inhibits the release of histamine from depolarized slices of rat brain [4].

Although three histamine receptors have been studied extensively from the pharmacologic point of view [5,6], the biochemical nature of histamine receptors are incompletely characterized. Furthermore, growing evidence suggests that complex and heterogenous activities of histamine in vitro and in vivo cannot be explained by three subtypes of histamine receptors alone. Therefore the purpose of this article is to delineate the heterogenous actions of histamine biochemically, and to understand how a single biogenic amine is capable of inducing a variety of different cellular functions under different circumstances.

Heterogeneity of Histamine Metabolism Histamine in tissues is derived from the decarboxylation of histidine in a single step by histidine decarboxylase (HDC) (Fig 1). A number of studies suggest that HDC is not a homogenous enzyme, in which multiple isoforms of HDC exhibitions with different isoelectric points have been reported [7,8]. This heterogeneity of HDC is further supported by the evidence that at least two different HDC cDNA have been cloned that show 86.1% homology in their amino acid sequences [9,10]. Furthermore, histamine is also derived from histidine by aromatic-L-amino acid decarboxylase (DOPA decarboxylase, DDC) [11]. Amino acid sequence analysis suggests that the NH_2-terminal 483 amino acid residues of the cloned rat HDC [9] shared 52% and 53% identities with those of rat DDC [12] and guinea-pig DDC [13], respectively.

Histamine is released in conjunction with other potent chemical mediators in response to specific IgE-mediated [14] or non-specific mechanisms [15] from the tissue mast cells [16] or blood basophilic leukocytes [17]. Released histamine is then catabolized by either diamine oxidase (DAO) or histamine-N-methyltransferase (HMT) [11] (Fig 1). The dominant pathways are different in various species and in different organs/tissues. For example, HMT is the major pathway in mammalian brain, whereas DAO is the main metabolic pathways in the nervous system of some invertebrates [11].

Heterogeneity of H_1 Receptors An early demonstration of the presence of the H_1 receptor on the membrane fractions of guinea pig ileum smooth muscle was carried out by Hill et al [18] using the radiolabeled H_1-specific antagonist [^{3}H]-pyrilamine. The dissocia-

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Abbreviations:
AC: adenylyl cyclase
cAMP: cyclic adenosine monophosphate
DAO: diamine oxidase
DDC: DOPA decarboxylase
DPPE: N,N-diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine-HCl
EC_{50}: a half maximal concentration
HDC: histidine decarboxylase
HMT: histamine-N-methyltransferase
HPLC: high-performance liquid chromatography
IP_3: inosital trisphosphate
kd: dissociation constant
PCR: polymerase chain reaction
PIP_2: phosphatidylinositol diphosphate
PKC: protein kinase C
PLC: phospholipase C
SDS-PAGE: sodium dodecyl sulfate polyacrylamide gel electrophoresis
SHT: 5-hydroxytryptamine

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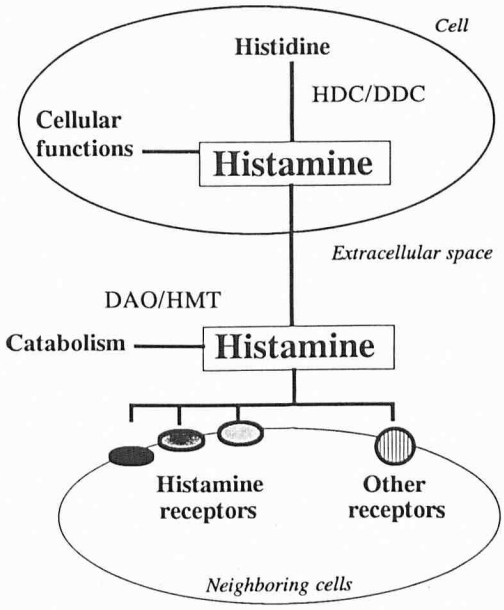

Figure 1. Heterogenous activities of histamine. Histamine is synthesized by histidine decarboxylase (HDC) or DOPA decarboxylase (DDC), and catabolized by either diamine oxidase (DAO) or histamine-N-methyltransferase (HMT). Synthesized intracellular histamine may induce cellular functions such as cell proliferation and platelet aggregation, whereas released histamine binds to at least three different histamine specific receptors (H_1, H_2, and H_3 receptors), and is also capable of activating other related receptors like serotonin 1c receptors.

tion constant (K_d) from [^{3}H]-pyrilamine binding studies correlated with the EC_{50} of the contractile response of guinea pig ileum to histamine, suggesting that [^{3}H]-pyrilamine binding sites were the specific H_1 receptor. However, a similar number of [^{3}H]-pyrilamine binding sites were demonstrated on rat, guinea pig, and rabbit ileal membranes, although the contractile effects of histamine varied widely in these species [19]. The K_d of [^{3}H]-pyrilamine also varied widely, from 0.7 nM to 219 nM in various tissues [20]. The difference of activity of H_1 antagonists was also demonstrated in functional assays, such as smooth muscle contraction, Ca^{++} mobilization, glycogen hydrolysis, prostaglandin E synthesis, ion transport, Ca^{++} efflux, and cGMP formation, with an IC_{50} ranging from 30 pM to 10 μM [20]. Moreover, subclasses of the H_1 receptor were detected in various tissues using different radiolabeled ligands [20].

[^{3}H]-pyrilamine binding studies indicate that extracellular Na^+, Mg^{++}, Mn^{++}, and guanine nucleotides selectively alter the agonist affinity in guinea pig brain membranes [21], and dithiothreitol also increased agonist affinity in guinea pig ileum [22]. This might suggest that the heterogeneity of the H_1 receptors is due to the microenvironments in which the H_1 receptor is present, or the additional interaction with G-proteins, as demonstrated with other G-protein–coupled membrane receptors [23].

In our previous studies, we have shown that during cellular differentiation of cultured BC3H1 smooth muscle cells, the K_d and the receptor number for [^{3}H]-pyrilamine binding were transiently decreased from 276 nM to 46.5 nM, and from 13.3×10^6/cell to 2×10^6/cell, respectively [24]. Data from saturation binding experiments indicate that the high-affinity H_1 receptor on differentiated cells was converted to the low-affinity receptor by the incubation of BC3H1 cells with glycosylation inhibitors, tunicamycin, or swainsonine without a significant change in receptor number [24]. Tunicamycin and swainsonine had no effect on the K_d of the low-affinity H_1 receptor on undifferentiated cells. Concanavalin A, wheat germ agglutinin, lentil lectin, and phytohemagglutinin, which bind to carbohydrate molecules, also inhibited [^{3}H]-pyrilamine binding on differentiated cell membranes, but had no effect on undifferentiated cell membranes [24]. The molecular weight of the H_1 receptor on differentiated cells was approximately 68,000 as analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), which after treatment with N-glycanase was shifted to 40,000, a molecular weight similar to that of the H_1 receptor on undifferentiated cells [24]. These results suggest that one element contributing to the H_1-receptor heterogeneity is receptor N-glycosylation.

Ruat et al [25] have used irreversible photoaffinity labeling to specifically label H_1-binding proteins in cell membranes. They synthesized [^{125}I]-iodoazidophenpyramine, a highly potent H_1 receptor antagonist derived from pyrilamine. Upon irradiation, 5% of the bound radioactivity was covalently incorporated into the H_1 receptor of guinea pig brain membranes. SDS-PAGE analysis indicated that the molecular weight of the H_1 receptor was 350,000–400,000 dalton in the absence of 2-mercaptoethanol, and the molecular weight decreased to 56,000 and 47,000 in the presence of 2-mercaptoethanol. This suggests that the H_1 receptor may have one or more disulfide bridges, resulting in a higher molecular weight complex. Furthermore, in the presence of protease inhibitors, labeling of the 56,000-dalton peptide increased at the expense of the 47,000-dalton peptide. This also suggests that the 47,000-dalton peptide is a proteolysis product of the 56,000-dalton peptide. In our previous studies, the protein with [^{3}H]-pyrilamine binding activity was purified with gel filtration, chromatofocusing followed by reverse-phase high-performance liquid chromatography (HPLC) from hamster vas deferens DDT1MF-2 cells [26]. The final material was a single peak on reverse-phase HPLC and a single band of apparent molecular weight 39,000 daltons on SDS-PAGE, which exhibited specific [^{3}H]-pyrilamine binding activity. This molecular weight of the H_1 receptor on DDT1MF-2 is smaller than that reported by Ruat et al [25], and might also be due to proteolytic degradation. Furthermore, as described above [24], part of the difference of molecular weight might also be due to receptor glycosylation.

The H_1 receptor is known to be coupled to phosphatidylinositol hydrolysis pathways, in which the H_1 receptor-specific stimulation induced hydrolysis of phosphatidylinositol with formation of inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol, leading to intracellular Ca^{++} mobilization and activation of protein kinase C (PKC) [1]. Recent molecular cloning studies have identified multiple subtypes of PKC [27]. Therefore, action of PKC after stimulation with the H_1 receptor may be varied in different cells depending upon the cellular components of PKC subtypes (Fig 2).

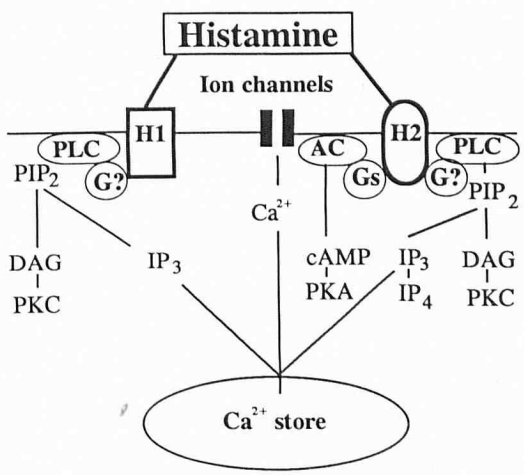

Figure 2. Functional diversity of the H1 and H2 receptors. The H_1 receptor is coupled to unidentified G proteins (G?), which activate phospholipase C (PLC) followed by hydrolysis of phosphatidylinositol diphosphate (PIP_2) to 1,4,5-inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 induces CA^{++} mobilization from intracellular stores, and DAG is known to activate protein kinase C (PKC). The H_2 receptor is capable of activating both adenylyl cyclase (AC) and PLC by coupling to two different G proteins (Gs and G?).

A number of phosphatidylinositol-coupled Ca^{++}-mobilizing receptors have been already cloned, and sequence homology analysis indicates the striking homology among these receptor cDNA. Therefore, the H_1 receptor cDNA will be cloned by a low-stringency hybridization technique or polymerase chain reaction (PCR) in the near future.

Functional Heterogeneity of H_2 Receptors As described above, H_1 receptors are known to be coupled to phosphatidylinositol hydrolysis pathways, whereas the H_2 receptor is coupled to adenylate cyclase with histamine-stimulating increases in intracellular cyclic adenosine monophosphate (cAMP) [3]. Both the H_1 and H_2 receptors are co-localized in various cells/tissues, and regulate histamine responses via secondary Ca^{++} and cAMP pathways, respectively [28].

In neutrophils, H_2-specific stimulation consistently enhances the chemokinetic response, whereas the chemotactic response was inhibited in a H_2-receptor–dependent manner [29,30]. Although the inhibition of chemotaxis is due to the elevation of cAMP, the mechanism of the H_2-receptor–mediated stimulation of chemokinesis is not explained by the activation of secondary cAMP pathways. This suggests that the H_2 receptor could have multiple independent effects on steps early in neutrophil activation.

Chew reported that the H_2-receptor stimulation not only activated cAMP pathways, but also increased $[Ca^{++}]_i$ in parietal cells [31]. In our previous studies, we have also shown that histamine increased $[Ca^{++}]_i$ in human HL-60 granulocytic cells in a dose-dependent manner with a half-maximal concentration (EC_{50}) of approximately 10^{-6}–10^{-5} M, which exhibited H_2-receptor specificity [32]. The cell-permeable form of cAMP and forskolin failed to increase $[Ca^{++}]_i$ [32]. Because the H_2 agonist, 4-methyl histamine-induced mobilization of $[Ca^{++}]_i$ was not diminished by reducing the concentration of extracellular Ca^{++} nor by the addition of Ca^{++} channel antagonists, $LaCl_3$ and nifedipine, we found $[Ca^{++}]_i$ mobilization was due to the release of Ca^{++} from intracellular stores. Furthermore, histamine increased the levels of IP_3 [32], suggesting that the H_2 receptor is capable of activating phosphatidylinositol hydrolysis pathways like the H_1 receptor. Interestingly, histamine-induced Ca^{++} mobilization was inhibited by the preincubation with cholera toxin, but not by pertussis toxin. Cholera toxin is known to irreversibly activate Gs protein, resulting in increasing intracellular cAMP. Therefore, the H_2 receptor on HL-60 cells may be coupled to two different cholera-toxin–sensitive G-proteins, and activate adenylate cyclase and phospholipase C simultaneously (Fig 2).

The H_2 receptor-mediated intracellular signaling pathways can be altered by modification of the ligand. For example, histamine albumin conjugates, which were used to identify the H_2 receptor-bearing leukocytes for many years [33], have been shown to act as active ligands and increase the level of $[Ca^{++}]_i$ in HL-60 cells in an H_2-receptor–specific manner [34]. Both histamine and histamine-albumin conjugates specifically desensitized each other, but the chemotactic peptide fMLP failed to interact with both ligands, although histamine and fMLP increased $[Ca^{++}]_i$ to a similar degree in HL-60 cells [34]. However, unlike histamine, histamine-albumin–induced $[Ca^{++}]_i$ mobilization was sustained for more than 10 min as a result of Ca^{++} influx [34]. The H_2 receptor has been shown to interact with Ca^{++} channels as a result of cAMP-dependent phosphorylation of Ca^{++} channels in other systems [35]. However, in HL-60 cells, the H_2 receptor-specific stimulation failed to activate $^{45}Ca^{++}$ influx, although histamine has been shown to increase cAMP in the H_2-receptor–specific manner [36]. More interestingly, the level of 1,3,4,5-IP_4 was also high and sustained after stimulation with histamine-albumin conjugates [37]. As IP_4 has been shown to activate Ca^{++} channels [38], histamine-albumin–induced Ca^{++} influx may be due to the altered metabolism of IP_3, rather than to cAMP-mediated phosphorylation of Ca^{++} channels.

Recently, the cDNA for the H_2 receptor has been cloned using a PCR approach from gastric parietal cells [39]. Its amino acid sequence is shorter than other G-protein–coupled receptor sequences, but exhibits similar structural motifs, in which the peptide spans the membrane seven times with an extracellular NH_2-terminal and intracellular COOH-terminal. Furthermore, the first extracellular domain contains a possible N-glycosylation site, and cysteine residues are found in both the second and the third extracellular domains [39]. However, Northern blot analysis shows that mRNA of the H_2 receptor is not detectable in heart, whereas the H_2 receptor mediates a positive chronotropic effect in right atria [40] and a positive inotropic effect in ventricle via cAMP [41]. As recent gene cloning techniques have identified more isoforms of receptor genes than would have been expected from the known pharmacology of those receptors, such as muscarinic acetylcholine receptors [42], GABA receptors [43], and glycine receptors [44], more subtypes of the H_2 receptor may be identified in the future.

Cross-talk Between Histamine and Serotonin Receptors Serotonin (5-hydroxytryptamine, 5HT) and histamine are biogenic amines with similar structure and similar biologic activities. Extensive pharmacologic studies using various synthetic agonists and antagonists have demonstrated that both 5HT and histamine exert physiologic and pathologic activities through binding to their specific cell-surface receptors. However, it is not well characterized whether 5HT and histamine react only with their own specific receptors, or whether under certain circumstances these ligands functionally cross-react with each other. Such analyses are difficult because most cells/tissues express various subtypes of 5HT and histamine receptors on their cell surface.

Although the H_1 receptor cDNA has not been cloned, three serotonin receptor cDNA (5HT1a, 5HT1c, and 5HT2b) have been cloned using a unique Xenopus oocyte expression system [45] and low-stringency cross-hybridization techniques [46,47]. Because the 5HT1c and the H_1 receptors are known to share common intracellular phosphatidylinositol hydrolysis pathways, a system that allows the functional expression of 5HT1c cDNA is a good model for the further analysis of cross-reactivity between 5HT and histamine. In our previous study [48], the RNA for the 5HT1c receptor was transcribed in vitro from the cloned 5HT1c receptor cDNA, and was injected into Xenopus oocytes in order to study 5HT1c receptor responses to various biogenic amines. As a result, histamine and the H_1 receptor agonists, but not the H_2 and H_3 agonists, significantly induced $^{45}Ca^{++}$ efflux in 5HT1c-receptor-RNA-injected oocytes, but not in uninjected and water-injected oocytes. However, the H_1, H_2, and H_3 antagonists failed to inhibit histamine-induced $^{45}Ca^{++}$ efflux at 10^{-6} M. This clearly suggests that the 5HT1c receptor can be stimulated by histamine, although its action is different from "classical" histamine pharmacology.

Histamine as an Intracellular Messenger Action of released histamine was believed to be mediated by various subtypes of histamine receptors as described above. However, because HDC activity and intracellular concentrations of histamine have been correlated with cell growth [49], intracellularly synthesized histamine may have a role in cell growth and tissue repair. More recently, Saxena et al [50] reported that inhibitors of HDC suppressed phorbol ester- or collagen-induced platelet aggregation, which was reversed by the novel histamine non-H_1, non-H_2, non-H_3 antagonist, N,N-diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine-HC1 (DPPE). Furthermore, in saponin-permeabilized platelets, added histamine reversed the inhibition by DPPE or HDC inhibitors on platelet aggregation. These data suggest a role for histamine as an intracellular messenger, although it is still unclear whether histamine reacts with intracellular receptors.

CONCLUSION

Histamine is capable of inducing a wide variety of cellular functions through its heterogenous receptors, or by direct action in the cytosol by interacting with other multiple factors. In order to understand the complex actions of histamine in biology and medicine, more studies are required, and perhaps new approaches should be established, in which multiple phenomena can be monitored simultaneously.

REFERENCES

1. Hill SJ: Distribution, properties, and functional characteristics of three classes of histamine receptor. Pharmacol Rev 42:45–83, 1990
2. Ash ASF, Schild HO: Receptors mediating some actions of histamine. Br J Pharmacol 27:427–439, 1966
3. Black JW, Duncan WAM, Durant CJ, Ganellin CR, Parsons EM: Definition and antagonism of histamine H2 receptors. Nature 236:385–390, 1972
4. Arrang JM, Garbarg M, Lancelot LC, et al: Highly potent and selective ligands for histamine H3-receptor. Nature 327:117–123, 1987
5. Beaven MA: Histamine. N Engl J Med 294:30–36, 1976
6. Beaven MA: Histamine. N Engl J Med 294:320–325, 1976
7. Savany A, Cronenberger L: Properties of histidine decarboxylase from rat gastric mucosa. Eur J Biochem 123:593–599, 1982
8. Watanabe T, Wada H: In: Parvez S, Nagatsu T, Nagatsu I, Parvez H (eds.). Methods in Biogenic Amine Research. Elsevier, Amsterdam, 1983, pp 689–720
9. Joseph DR, Sullivan PM, Wang Y-M, et al: Characterization and expression of the complementary DNA encoding rat histidine decarboxylase. Proc Natl Acad Sci USA 87:733–737, 1990
10. Yamamoto J, Yatsunami K, Ohmori E, et al: cDNA-derived amino acid sequence of L-histidine decarboxylase from mouse mastocytoma P-815 cells. FEBS Lett 276:214–218, 1990
11. Green JP, Prell GD, Khandelwal JK, Blandina P: Aspects of histamine metabolism. Agents Actions 22:1–15, 1987
12. Tanaka T, Horio H, Taketoshi M, et al: Molecular cloning and sequencing of a cDnA of rat dopa decarboxylase: partial amino acid homologies with other enzymes synthesizing catecholamines. Proc Natl Acad Sci USA 86:8142–8146, 1989
13. Taketoshi M, Horio Y, Imamura I, Tanaka T, Fukui H, Wada H: Molecular cloning of guinea-pig aromatic-L-amino acid decarboxylase cDNA. Biochem Biophys Res Commun 170:1229–1235, 1990
14. Ishizaka T: Role of GTP-binding protein in histamine release from mast cells. Clin Immunol Immunopath 50:20–29, 1989
15. Morrison DC, Roser JF, Cochranw CG, Hensen PM: Two distinct mechanisms for the initiation of mast cell degranulation. Int Archs Allergy Appl Immun 49:172–178, 1975
16. Riley JF, West GB: In: Rocha e Silva M (ed.). Handbook of Experimental Pharmacology. Springer-Verlag, New York, 1966, pp 116–135
17. Merget RD, Maurer AB, Koch U, et al: Histamine release from basophils after in vivo application of recombinant human interleukin-3 in man. Int Arch Allergy Appl Immunol 92:366–374, 1990
18. Hill SJ, Young JM, Marrian DH: Specific binding of ^{3}H-mepyramine to histamine H1 receptors in intestinal smooth muscle. Nature 270:361–363, 1977
19. Chang RSL, Tran VT, Snyder SH: Characteristics of histamine H1-receptors in peripheral tissues labelled with [^{3}H]-mepyramine. J Pharmacol Exp Ther 209:437–442, 1979
20. Mitsuhashi M, Payan DG: Molecular and cellular analysis of histamine H1 receptors on cultured smooth muscle cells. J Cell Biochem 40:183–192, 1989
21. Chang RSL, Snyder SH: Histamine H1-receptor binding sites in guinea-pig brain membranes: regulation of agonist interactions by guanine nucleotides and cations. J Neurochem 34:916–922, 1980
22. Donaldson J, Hill SJ: 1,4-Dithiothreitol-induced changes in histamine H1-agonist efficacy and affinity in the longitudinal smooth muscle of guinea-pig ileum. Br J Pharmacol 90:263–271, 1987
23. Koo C, Lefkowitz RJ, Snyderman R: Guanine nucleotides modulate the binding affinity of the oligopeptide chemoattractant receptor on human polymorphonuclear leukocytes. J Clin Invest 72:748–753, 1983
24. Mitsuhashi M, Payan DG: Receptor-glycosylation regulates the affinity of histamine H1 receptors during smooth muscle cell differentiation. Mol Pharmacol 35:311–318, 1989
25. Mitsuhashi M, Payan DG: Solubilization and purification of the pyrilamine binding protein from cultured smooth muscle cells. Mol Pharmacol 35:751–759, 1989
26. Ruat M, Korner M, Garbarg M, et al: Characterisation of histamine H1-receptor binding peptides in guinea-pig brain using [^{125}I]iodoazidophenpyramine, an irreversible specific photoaffinity probe. Proc Natl Acad Sci USA 85:2743–2747, 1988
27. Boyer JL, Hepler JR, Harden TK: Hormone and growth factor receptor-mediated regulation of phospholipase C activity. Trends Pharmacol Sci 10:360–364, 1989
28. Garbarg M, Schwartz JC: Synergism between histamine H1- and H2-receptors in the cyclic AMP responses in guinea-pig brain slices: effects of phorbol esters and calcium. Mol Pharmacol 33:38–43, 1988
29. Anderson R, Glover A, Rabson AR: The in vitro effects of histamine and metiamide on neutrophil motility and their relationship to intracellular cyclic nucleotide levels. J Immunol 118:1690–1696, 1977
30. Seligman BE, Fletcher MP, Gallinm JI: Histamine modulation of human neutrophil oxidase metabolism, locomotion, degranulation, and membrane potential changes. J Immunol 130:1902–1909, 1983
31. Chew CS: Cholecytokinin, carbachol, gastrin, histamine, and forskolin increase $[Ca^{2+}]_i$ in gastric glands. Am J Physiol 250:G814–G823, 1986
32. Mitsuhashi M, Mitsuhashi T, Payan DG: Multiple signaling pathways of histamine H2 receptors. Identification of an H2 receptor-dependent Ca^{2+} mobilization pathway in human HL-60 promyelocytic leukemia cells. J Biol Chem 264:18356–18362, 1989
33. Melmon KL, Bourne HR, Weinstein Y, Sela M: Receptors for histamine can be detected on the surface of selected leukocytes. Science 177:707–709, 1972
34. Mitsuhashi M, Mitsuhashi T, Dazin PF, Payan DG: Agonistic activities of histamine-albumin conjugates to histamine H2 receptors on human HL-60 promyelocytic leukemia cells. Mol Pharmacol 40:271–275, 1991
35. Levi RC, Alloatti G: Histamine modulates calcium current in guinea-pig ventricular myocytes. J Pharmacol Exp Ther 246:377–383, 1988
36. Gespach C, Saal F, Cost H, Abita J-P: Identification and characterization of surface receptors for histamine in human promyelocytic leukemia cell line HL-60. Comparison with human peripheral neutrophils. Mol Pharmacol 22:547–553, 1982
37. Mitsuhashi M, Payan DG: Multiple signaling pathways of histamine H2 receptors. Agents Actions 33:289–294, 1991
38. Berridge MJ, Irvine RF: Inositol phosphates and cell signalling. Nature 341:197–205, 1989
39. Gantz I, Schaffer M, DelValle J, et al: Molecular cloning of a gene encoding the histamine H2 receptor. Proc Natl Acad Sci USA 88:429–433, 1991
40. Levi R, Owen DAA, Trzeciakowski J: Action of histamine on the heart and vasculature. In: Ganellin R, Parson M (eds.). Pharmacology of histamine receptors. J. Wright and Sons, Ltds., London, 1982, pp 236–297
41. Steinberg MI, Holland DR: Separate receptors mediating the positive inotropic and chronotropic effect of histamine in guinea-pig atria. Eur J Pharmacol 34:95–104, 1975
42. Barnard EA: Molecular neurobiology. Separating receptor subtypes from their shadows. Nature 335:301–302, 1988
43. Levitan ES, Schofield PR, Burt DR, et al: Structural and functional basis for GABAA receptor heterogeneity. Nature 335:76–79, 1988
44. Akagi H, Miledi R: Heterogeneity of glycine receptors and their messenger RNAs in rat brain and spinal cord. Science 242:270–273, 1988
45. Julius D, MacDermott AB, Axel R, Jessell TM: Molecular characterization of a functional cDNA encoding the serotonin 1c receptor. Science 241:558–564, 1988
46. Fargin A, Raymond JR, Lohse MJ, Kobilka BK, Caron MG, Lefkowitz RJ: The genomic clone G-21 which resembles a β-adrenergic receptor sequence encodes the 5-HT_{1A} receptor. Nature 335:358–360, 1988
47. Pritchett DB, Bach AW, Wozny M, et al: Structure and functional expression of cloned rat serotonin 5HT-2 receptor. EMBO J 7:4135–4140, 1988
48. Shichijo S, Payan DG, Harrowe G, Mitsuhashi M: Histamine effects on the 5HT1c receptor expressed in Xenopus oocytes. J Neurosci Res 30:316–320, 1991
49. Kahlson G, Rosengren E: Biogenesis and physiology of histamine. Edward Arnold Ltd, London, 1971
50. Saxena SP, Brandes LJ, Becker AB, Simons KJ, Labella FS, Gerrard JM: Histamine is an intracellular messenger mediating platelet aggregation. Science 243:1596–1599, 1989